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Presurgical assessment of memory-related brain structures: the Wada test and functional neuroimaging

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Medial temporal lobe structures are known to play a major role in memory processing. Recent work has revealed that extratemporal structures (e.g. the frontal lobe and thalamus) may also be important in memory function. In candidates for epilepsy surgery, particularly in those with temporal lobe seizures, presurgical evaluation of memory function is essential, since seizures may originate in the neural substrate that is critical for memory. In this article, we review the tools used for presurgical evaluation and their contribution to the understanding of memory function, focusing on the Wada test, [^{18}F]fluorodeoxy-glucose positron emission tomography ([^{18}F]FDG-PET) and functional magnetic resonance imaging (fMRI). We also explore perspectives on future studies that may elucidate the role of the temporal and extratemporal structures in memory function and the mechanisms of cerebral plasticity.

Key words: Wada test; intracarotid amobarbital procedure; memory; temporal lobe epilepsy; epilepsy surgery; functional neuroimaging; positron emission tomography; functional magnetic resonance imaging.

INTRODUCTION

The areas responsible for memory function in humans have been explored substantially over the last several decades. Using electrical stimulation, Penfield mapped not only motor and somatosensory areas of the human cortex but also cortical areas that subserve speech, vision and memory function during awake craniotomies for epilepsy surgery[1]. Scoville and Milner first reported severe anterograde amnesia following bilateral temporal lobectomy[2]. This pioneering work in patients with epilepsy confirmed the critical role of the hippocampi and adjacent temporal lobe systems in memory. Subsequent clinical and experimental studies have shown that medial temporal lobe structures play a major role in memory processing[3–5]. In addition, recent work on both humans and non-human primates has revealed that extratemporal structures (e.g. the frontal lobe and thalamus) may also be important in memory function[6–10]. Various methodologies are currently available for the investigation of those brain areas that subserve memory function. However, many issues concerning memory in patients with epilepsy remain unresolved.

The Wada test (intracarotid amobarbital procedure) is part of presurgical neuropsychological assessment in many centres. It is used to identify the hemisphere dominant for language and to evaluate memory function supported by either hemisphere after anaesthetising each one individually[11–13]. Memory testing during this reversible state is a model of the effects of the proposed temporal lobectomy, as it provides an estimate of how well memory functions will be supported after a unilateral resection.

Presurgical evaluation for epilepsy surgery aims to identify the area of focal dysfunction as well as the epileptic focus[14]. Over the last two decades, new evaluation tools based on neuroimaging techniques have become relevant to epilepsy surgery programmes. This, in turn, has offered the unique opportunity to examine brain function in epileptic patients by comparing various structural and functional

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methodologies. This integration of data from converging methods is of particular interest for exploring memory processing. However, few authors have reported systematic neuroimaging studies on memory function using different functional methods.

The purpose of this article is:

(i) To review the tools used for presurgical evaluation of epilepsy and their contribution to the understanding of memory function. We will focus on functional techniques which include the Wada test and functional neuroimaging, especially [^{18}F]fluorodeoxy-glucose positron emission tomography ([^{18}F]FDG-PET) and functional magnetic resonance imaging (fMRI).

(ii) To suggest perspectives on studies of memory-related brain structures through presurgical evaluation of epilepsy patients. We will discuss topics relevant to epilepsy surgery and general aspects of memory function such as the contribution of the frontal lobe and cerebral plasticity. This approach will seek to provide a framework for future research in the general population as well as in patients with epilepsy.

EVALUATION OF EPILEPSY SURGERY CANDIDATES

Approximately 50% of all patients with epilepsy suffer from focal seizures, and 20% of these are inadequately controlled with antiepileptic drugs. Under the most conservative estimate, at least half of such patients are potential candidates for surgical therapy[15].

The most common surgically remediable epileptic syndrome is mesial temporal lobe epilepsy. Anterior temporal lobectomy together with selective amygdalohippocampectomy account for nearly 70% of all surgical interventions and render approximately 60% of operated patients seizure-free[15]. A recent randomised, controlled study showed that 58% of patients who underwent epilepsy surgery were free from seizures involving impairment of consciousness after a 1-year follow-up[16]. Considering the severity of epilepsy in the population that requires resective surgery, epilepsy surgery can be considered a very successful therapy[17,18].

The objective of resective surgery is the complete resection or disconnection of the epileptogenic zone. In order to achieve this, the location and anatomical boundaries of the epileptogenic zone need to be identified precisely. To this aim, comprehensive presurgical evaluation protocols are required and often include routine and sleep electroencephalograms (EEGs), video-EEG telemetry with scalp and/or intracranial electrodes, neuropsychological testing, and structural and functional neuroimaging[17].

Memory function and epilepsy surgery

While complete resection of the epileptogenic zone is indispensable for seizure relief, this aim is limited by one major restriction: sparing of eloquent cortex (cortex necessary for a given function) to avoid new disabling deficits after surgery[17]. In temporal lobe epilepsy, presurgical evaluation of memory function is essential, since seizures originate in the neural substrate that may be critical for memory. The neuropsychological profile of patients with temporal lobe epilepsy provides information on the localisation and lateralisation of brain dysfunction caused by epileptogenic lesions[13]. Presence of pathology in the dominant temporal lobe is typically associated with deficits involving verbal memory and word retrieval. When pathology is present in the non-dominant temporal lobe, impairment of visuospatial functioning and visual memory have been reported, although these deficits are more difficult to document than those of verbal skills. Information about individual baseline levels should be obtained to evaluate postoperative cognitive change. Material-specific memory loss has been demonstrated following anterior temporal lobectomy: verbal memory decline after surgery in the dominant hemisphere and visuospatial memory deficit in the non-dominant hemisphere[19]. As in case H.M. reported by Scoville and Milner[2], bilateral medial temporal lesions can cause profound anterograde memory impairment. Similar amnesia has also been observed in rare cases after unilateral anterior temporal lobectomy[20–23].

To predict and thus prevent unacceptable neuropsychological deficits after epilepsy surgery, it is important to identify presurgically those patients who are at high risk of developing postsurgical memory impairment. Such an approach could result in tailoring the resection to minimise the possible neuropsychological deficits.

PRESURGICAL EVALUATION TOOLS FOR MEMORY-RELATED BRAIN STRUCTURES

The Wada test

The Wada test relies on the induction of a ‘reversible lesion’ for evaluating lateralisation of speech and memory. Amobarbital injection into the internal carotid artery (ICA) pharmacologically inactivates the cortex supplied by the anterior and middle cerebral arteries in the hemisphere ipsilateral to the injection

for several minutes. During this period the patient is presented with multiple cognitive tasks[11, 12]. Throughout this article, right/left and ipsilateral/contralateral Wada scores refer to the side of the tested hemisphere (i.e. contralateral to the injection side).

In 1949, Wada reported the original procedure of the Wada test to identify the hemisphere of language dominance in patients with schizophrenia or schizoid personality disorders[24]. Thereafter, Wada and Rasmussen applied this technique to patients with epilepsy[11]. Milner *et al.* expanded the use of the Wada test to measure unilateral memory function in epilepsy surgery candidates in order to predict postoperative amnesia[12]. Since then, the contributions of the Wada test have been widely extended and include: (i) lateralisation of seizure focus[25–32]; (ii) prediction of seizure control outcome[29, 33–35]; and (iii) prediction of neuropsychological outcome[36–41]. On the other hand, its value to preclude postoperative amnesic syndromes still remains open to question[42, 43].

Despite its clinical usefulness, the Wada test has several major drawbacks, including morbidity risk due to the intracarotid cathetisation[44] and unavailability of data on test–retest reliability and validity[45]. It is sometimes difficult to interpret the results of the Wada test, since the evaluation is performed within a short period (approximately 3–5 minutes) under the behavioural effects of anaesthesia (e.g. aphasia, attention deficits, neglect and somnolence). A critical concern over its validity on memory assessment is that an injection of amobarbital via the ICA perfuses the uncus, amygdala and anterior hippocampus but not the posterior two thirds of the hippocampus[46]. It also inactivates the rest of the hemisphere including the frontal and temporal lobes ipsilateral to the injection[46]. To evaluate memory function in the posterior hippocampus, a selective Wada test with an amobarbital injection via the posterior cerebral artery was introduced[46]. However, this procedure carries a greater risk of morbidity than does ICA administration and thus is not widely used[47].

To date, the validity of the ICA procedure has been confirmed empirically by various findings. EEG background activity recorded by intrahippocampal depth electrodes was significantly suppressed in the posterior hippocampal regions even when amobarbital was not perfused into those areas[48]. The degree of hippocampal damage present in an epileptogenic hemisphere is significantly correlated with the impairment of Wada memory performance on the same hemisphere[49–52].

Structural neuroimaging

Although not usually considered as a functional technique, high-resolution MRI is now a requirement for presurgical evaluation and its findings have been found to correlate with those of functional techniques. Volumetric MRI can identify around 90% of patients with mesial temporal sclerosis, which is the most common cause of temporal lobe epilepsy[53].

With respect to testing memory function, MRI hippocampal volume correlates with baseline neuropsychological measures of memory[54–57]. A significant correlation between hippocampal volume asymmetries measured with MRI and Wada memory asymmetries has also been found[54, 58].

Although structural abnormalities in epileptic brains overlap with the areas of functional disturbance, structural MRI does not necessarily show the magnitude and extent of the dysfunction. Thus, structural MRI has recently been used together with functional techniques, including [^{18}F]FDG-PET, magnetoencephalography, event-related potentials and intracranial electrical stimulation of the cortex, for the precise identification of functionally relevant regions[53].

Functional neuroimaging

Functional neuroimaging employed in the evaluation of surgical candidates can non-invasively map brain functions. It mainly uses applications of magnetic resonance or isotope studies[53]. The former includes fMRI (see the description below) and magnetic resonance spectroscopy (MRS), which measures cerebral metabolites and neurotransmitters. Isotope studies allow mapping of regional cerebral blood flow (single-photon emission computed tomography and [^{15}O]H_2O-PET), glucose metabolism ([^{18}F]FDG-PET) and the distribution of receptors using the binding of specific ligands such as flumazenil, the central benzodiazepine-$GABA_A$ receptor complex ([^{11}C]flumazenil-PET).

In this review we will focus on [^{18}F]FDG-PET and fMRI, as these are the techniques most readily available during presurgical assessment to explore memory-related brain structures.

[^{18}F]FDG-PET

[^{18}F]FDG-PET can image the rate of cerebral glucose metabolism. During the interictal period, partial epilepsies usually show one or more regions of hypometabolism on [^{18}F]FDG-PET. In contrast, regional hypermetabolism or mixed hyper- and hypometabolic patterns are seen during seizures[59]. In 70–90% of patients with temporal lobe epilepsy, interictal [^{18}F]FDG-PET scans detect unilateral temporal hypometabolism or asymmetric bitemporal hypometabolism. Patients with restricted lesions such

as mesial temporal sclerosis may show widespread hypometabolic areas involving the lateral temporal neocortex, ipsilateral thalamus, basal ganglia, and frontal and parietal lobes[60–64]. Hypometabolism can be detected in the absence of structural abnormalities on MRI and/or histopathologic abnormalities in resected tissue[65].

Hypometabolism on [^{18}F]FDG-PET appears to reflect the loss of neurones in the damaged structures. However, it is not always correlated with the volume of structures involved[66] nor with neuronal density found in resected specimens[60, 67]. Such metabolic changes may be explained by alterations in synaptic organisation[68, 69] or reduced substrate uptake rather than supply[70]. Widespread hypometabolism may be associated with additional epileptogenic areas, effects of diaschisis or the sites of seizure propagation[71].

The hypometabolic temporal area in patients with temporal lobe epilepsy strongly correlates with clinical and neurophysiological findings[72, 73]. The presence of interictal temporal hypometabolism was associated with favourable postsurgical seizure control[66, 73–75]. As for cognitive function, patients with left mesial temporal lobe epilepsy, showing hypometabolism of the left hemisphere, tend to show verbal memory and word fluency impairments[9, 64]. Pelaez *et al.* compared per cent recall on the Wada test after unilateral injection with regional glucose metabolism on the side contralateral to the injection in patients with unilateral mesial temporal lobe epilepsy[76]. Although no linear correlation was found between per cent recall of Wada memory performance and the degree of glucose metabolism, the presence of memory failure, defined as less than 67% retention score, was predicted by the presence of hypometabolism in the left lateral, and right mesial and inferior temporal regions. Similarly, the hemisphere that fails the Wada test tends to be that which shows temporal hypometabolism[77, 78]. Hong *et al.* showed that the asymmetry index of glucose metabolism in the mesial temporal region correlated with the asymmetry index of Wada memory performance[79].

fMRI

fMRI represents neuronal activity indirectly via haemodynamic changes in the human brain. The size of the cortical area activated and the number of involved neurones directly influence the magnitude of the change in regional cerebral blood flow[80]. In principle, blood arriving in the activated region contains a higher proportion of diamagnetic oxyhaemoglobin and a lower proportion of paramagnetic deoxyhaemoglobin when compared with non-activated regions. The subtle blood-oxygen-level-dependent contrast in magnetic state results in a larger T2*signal from the activated region, which enables task-specific changes in regional cerebral blood flow to be visualised[81].

Since the late 1990s, fMRI has become the pre-eminent technique for the non-invasive topographic study of human brain activity. Mapping of sensory and motor functions with fMRI has been fairly well established in both normal controls and patients[82]. An important use of this technique for epilepsy is to delineate areas of the brain that are responsible for specific functions, such as the primary sensory and motor cortex, and to identify their anatomical relation to the areas to be removed by the proposed surgical resection[53, 83].

Mapping of language function with fMRI has also been established. Various types of language tasks predominantly activate the frontal language areas in both neurologically normal[84, 85] and epileptic subjects[85–89]. Unilateral activation of the lateral or inferior frontal cortex identified by fMRI has been in excellent agreement with laterality determined by cortical stimulation mapping[89, 90] or the Wada test[85–89].

More recently, fMRI studies with memory-related tasks have demonstrated consistent activation of medial temporal structures and the frontal cortex (ventrolateral, dorsolateral and prefrontal regions) in normal subjects[10, 91, 92]. The pattern of activation in such regions is process-specific (encoding/retrieval) and material-specific (verbal/non-verbal). Both frontal and medial temporal activation obtained with encoding tasks appear to be lateralised according to the test material: left-sided activation with verbal material and right-sided with non-verbal material[10, 93]. Activation of medial temporal structures has been localised to more posterior regions by encoding tasks and more anterior regions by retrieval tasks[91, 92]. These localisation and lateralisation within distinct regions are, however, not always clear-cut: activation can be multifocal or bilateral. They are also affected by the combination of target and control tasks, subsequent memory (remembered/forgotten), and nature of stimuli and mnemonic strategies (e.g. novelty, familiarity and meaningfulness)[10, 91–93]. In addition, the pattern and degree of activation appear to differ depending on the order of stimulus presentation, which either follows a block design paradigm (blocks of trials that group tasks with the same condition are presented sequentially) or an event-related paradigm (trials which consist of a single task are presented randomly)[94, 95].

For fMRI examination of a particular mental function, two critical issues should be considered[96]. First, the activation task used may engage various brain systems simultaneously, including sensory, motor and attention systems. Activation of these systems, therefore, must be compared with a contrast or baseline task. Secondly, some areas engaged by the tasks may

play a minor supportive role rather than a critical function. Conversely, lack of activation in a given region does not necessarily indicate an unimportant functional role for the region. Thus, the extent of the activation for each task must be validated empirically with more conventional measures.

In contrast to the rapid progress in memory studies with fMRI in normal subjects, there have been only a small number of studies in patients with epilepsy. Memory studies with fMRI could contribute to presurgical evaluation by identifying the relevant eloquent cortex for memory processing. Detre *et al.* first demonstrated that activation of posterior medial temporal regions during an environmental scene-encoding task relative to a spatially scrambled picture predicts memory lateralisation in 10 patients with temporal lobe epilepsy[97]. fMRI lateralisation scores of the posterior medial temporal activation corresponded closely with lateralisation indices of the memory score in the Wada test. More recently, Jokeit *et al.* have studied the lateralising value of fMRI activation, using Roland's Hometown Walking test as an activation task and covert counting of odd numbers starting with 21 as a baseline task[98]. This task demands conscious recollection of visuospatial information from long-term memory and is believed to activate the parahippocampal gyrus bilaterally. Medial temporal activation was higher in the hemisphere contralateral to the side of seizure onset and correctly classified the side of seizure focus in 90% of patients. Furthermore, the number of activated voxels within the left medial temporal lobe was positively correlated with Wada memory performance in the left hemisphere.

PERSPECTIVES ON FUTURE STUDIES OF MEMORY-RELATED BRAIN STRUCTURES

Prediction of neuropsychological outcome after surgery

The most consistent neuropsychological change after temporal lobe resective surgery is a decline in verbal memory after a temporal lobectomy in the dominant hemisphere. Changes in verbal memory function depend on the preoperative ability status: higher preoperative performance relates to greater losses[99, 100]. Furthermore, an earlier onset and a shorter duration of epilepsy as well as a younger age at surgery result in a better outcome[100–102]. Correlations between the postoperative neuropsychological outcome and volumetrically or histopathologically estimated hippocampal lesions have been reported[56, 103, 104]. The degree of neuropsychological deterioration after surgery is also determined by the volume of the resection and the degree of postsurgical seizure control[19, 99, 105]. There are, however, high-risk patients who do not show the expected deterioration in memory after surgery. This individual variability in memory change after anterior temporal lobectomy is incompletely understood[106].

In attempting to explain memory decline after anterior temporal lobectomy, reference is frequently made to the theories of functional adequacy and functional reserve[107]. In the first model, postsurgical memory deficits are thought to be dependent on the functional adequacy of the tissue to be resected. In studies using volumetric MRI and histopathology, the degree of postsurgical impairment in memory function was inversely correlated with the degree of structural damage to medial temporal lobe structures[56, 103]. In addition, higher preoperative performance on the memory measurements and larger extent of the resection are associated with greater memory decrements after surgery[99, 105, 108]. These findings provide indirect support for the model. On the other hand, the functional reserve model suggests that postsurgical memory deficits depend on the capacity or functional reserve of the contralateral temporal lobe to support memory functions following surgery. The occurrence of amnesic syndrome after unilateral anterior temporal lobectomy in patients with an occult lesion in the contralateral temporal lobe strongly supports this model[20, 22, 23]. It is also supported by the finding that patients with bilateral hippocampal volume loss undergoing left anterior temporal lobectomy show greater verbal memory decline than those with unilateral hippocampal atrophy[109]. Clinical observations have shown that neither model can fully explain individual differences in postsurgical memory outcome.

One would expect that findings from the Wada test would provide more direct evidence on this issue. Although Wada memory performance has proven useful to predict memory outcome, some studies reported that Wada memory performance in the ipsilateral hemisphere predicts memory outcome (i.e. functional adequacy model)[37, 107], whereas others reported that contralateral Wada memory performance is more predictive of memory outcome (i.e. functional reserve model)[36, 38, 39].

Functional neuroimaging may provide direct evidence of memory competence in the relevant brain structures. A [^{18}F]FDG-PET study has shown that the degree of glucose metabolism can predict postoperative neuropsychological outcome[110]. Patients who underwent a left (dominant) anterior temporal lobectomy with mild or no preoperative PET asymmetry showed substantially higher postoperative verbal memory decline than those with moderate or severe PET asymmetry (89% vs. 33%).

There has been a single report with fMRI on postoperative memory outcome[111]. Using a complex visual scene memory task, Casasanto *et al.* found a

significant positive correlation between the degree of asymmetry in the amygdalohippocampal activation and changes in recognition memory performance. Patients who had greater presurgical activation in the contralateral hemisphere showed postsurgical memory improvement, whereas those with greater presurgical activation in the ipsilateral hemisphere showed postsurgical memory decrement.

Deficits in visual memory have been demonstrated after non-dominant temporal resections[19]. Previous studies, however, have not yielded consistent findings in predicting cognitive changes after right anterior temporal lobectomy[108]. This may be in part due to the nature of the test material. Neuropsychological procedures, including the Wada test, may be more sensitive to verbal than non-verbal abilities. Similarly, correlation studies between [^{18}F]FDG-PET and neuropsychological measurements have failed to show a significant relation between glucose metabolism and visuospatial memory outcome[9, 64, 110]. fMRI memory tasks with less verbally encodable material might help predict non-verbal memory outcome, especially in patients with right temporal lobe epilepsy (see next section).

Effects of language dominance

Wada memory performance is affected by the laterality of language dominance. Memory scores on either hemisphere depend on the type of material presented[36, 112]. In left language dominant patients, the left (dominant) hemisphere shows higher memory scores with verbal material than with non-verbal (or dually encodable) material, whereas the right (non-dominant) hemisphere shows higher memory scores with non-verbal (or dually encodable) material than with verbal material, regardless of the side of seizure focus.

In one [^{18}F]FDG-PET study, patients with left mesial temporal lobe epilepsy showed additional areas of hypometabolism in the left inferior frontal gyrus (Broca's area) and the superior temporal gyrus at the parietotemporal junction, whereas such a pattern for hypometabolism was not present in those with right mesial temporal lobe epilepsy[64].

Verbal and non-verbal material has been used for memory activation in fMRI. One fMRI study using encoding tasks with four different types of material (words, faces, scenes and patterns) has revealed that the degree and laterality of activation is concordant with the nature of the material presented: encoding for words (verbal material) showed left activation, encoding for patterns (mostly non-verbal material) showed right activation, and encoding for faces and scenes (intermediate verbal material) showed broadly symmetrical activation[93]. In addition, neither verbalisability of material nor lateralisation of activation were found to be absolute, but rather to exist as a continuum[93]. These findings suggest that laterality of language dominance can significantly influence laterality of memory function and therefore it needs to be considered during memory tasks. For instance, in patients who have atypical language dominance due to early epileptogenic lesions in the left hemisphere, re-allocation of language and verbal memory to the right hemisphere can cause deficits of functions that are originally lateralised to the right hemisphere[113–115]. Moreover, the presence of atypical language dominance is higher in epileptic patients than in the general population[116, 117]. Further studies are required to investigate the interactions between memory function and language laterality, perhaps by combining results from the Wada test with functional neuroimaging.

False/reverse lateralisation

The laterality of Wada memory performance is based on the assumption that memory function mediated by medial temporal structures reflects the damage caused by or underlying epileptogenesis: intact performance on the non-epileptogenic side and impaired performance on the epileptogenic hemisphere[13]. Using absolute or comparative lateralising criteria of Wada memory performance from both hemispheres, 50–80% of patients with temporal lobe epilepsy are correctly lateralised[25–32]. In the remainder, Wada memory performance is symmetrical and therefore the laterality is indeterminate. A few patients with unilateral temporal lobe epilepsy, however, have been reported to show falsely/reversely lateralised Wada memory performance characterised by poorer memory performance in the non-epileptogenic hemisphere[26, 49, 79, 118]. Interestingly, one memory fMRI study using an environmental scene-encoding task has shown that fMRI lateralisation scores were concordant with memory lateralisation on the Wada test in two patients with false/reverse Wada memory asymmetry[97].

It is rare for [^{18}F]FDG-PET to falsely/reversely lateralise the epileptogenic hemisphere in unilateral temporal lobe epilepsy. Only a few patients with false/reverse lateralisation have been reported[119, 120]. [^{18}F]FDG-PET studies combined with the Wada test suggested that memory impairment contralateral to the hypometabolic zone never occurred[77], even in patients who were falsely/reversely lateralised by PET[120].

The false/reverse pattern of lateralisation may be caused by epilepsy-related factors (e.g. interictal epileptic discharges and subclinical seizures) or a

degree of bilateral temporal involvement. It is also possible that memory processing in these patients is atypical. It would be interesting to know whether memory profiles in falsely/reversely lateralised patients are different from those seen in correctly lateralised patients. Further studies will clarify the extent to which either hemisphere contributes to memory processing and what mechanism underlies a false/reverse pattern in the Wada test or functional neuroimaging.

Interhemispheric asymmetries and unilateral hemispheric values

Asymmetry indices for Wada memory scores have been used to predict the laterality of seizure focus[27–30, 32], postoperative seizure outcome[29, 33–35] and postoperative neuropsychological changes[36, 41]. Several studies have found that Wada memory asymmetry indices are more useful than unilateral measurements to identify the side of temporal damage. The use of asymmetry indices can determine the damaged hemisphere by comparison with the intact side, and thus control for individual differences in baseline levels[58, 121, 122]. However, asymmetry indices cannot be applied to patients who show bilaterally and symmetrically impaired memory competence. On the other hand, unilateral Wada memory performance has proven to reflect memory (dys-)function on either hemisphere[25, 36, 107]. It has not been well established whether ipsilateral, contralateral or asymmetrical Wada scores reflect the integrity of function-specific regions.

Similarly, [^{18}F]FDG-PET studies have used asymmetry indices of glucose metabolism using a regions-of-interest technique[9, 79]. This methodology allows comparison between glucose metabolism in the epileptogenic region and that in the homotopic contralateral cortex. Since asymmetry studies with regions of interest assume that the contralateral side is normal, it may be misleading in cases with bilateral hypometabolism. To obtain more informative lateralisation and localisation of memory-related brain structures, the application of an objective analytical approach, such as statistical parametric mapping, can be useful because it does not involve *a priori* hypotheses about extent and localisation of hypo- or hyper-metabolism and allows correlative studies with non-imaging variables such as memory performance[74, 123].

Asymmetry indices have also been used in fMRI studies for the determination of language and memory dominance[83, 96]. The use of asymmetry indices in fMRI studies decreases their capacity for high spatial resolution, which may provide useful information about spatial localisation and quantification of functional deficits related to distinct memory tasks.

For all these three techniques, it would be interesting to explore whether unilateral measurements can provide information additional to asymmetry indices and *vice versa*. This may be useful in evaluating surgical candidates, especially in patients with atypical language/memory dominance or atypical symmetrical temporal lobe functions, the very conditions whose outcome is most difficult to predict.

Contribution of the frontal lobe to memory processing

Recent neuroimaging studies have reported contributions of the frontal lobe to memory processing[7, 8, 10]. Kelley *et al.* have suggested that frontal lobe function is involved in memory performance during the Wada test[124]. In their previous fMRI study[6], encoding tasks produced dorsal frontal activation with various degrees of laterality according to the material used, and blood flow to the activated frontal regions was mainly supplied by the middle cerebral artery. The laterality of frontal activation in the fMRI study was highly concordant with the laterality of Wada memory performance. These results suggest that frontal regions also contribute to memory formation. This hypothesis offers a new viewpoint to the Wada test. Unfortunately, findings from neuroimaging and the Wada test were obtained separately in different subject populations: neuroimaging findings in normal subjects and Wada memory performance in patients with intractable epilepsy. This hypothesis requires further confirmation in the same population of patients with epilepsy.

As often pointed out, mild deficits of frontal lobe functions are difficult to detect with neuropsychological measurements[125, 126]. Jokeit *et al.* have shown that prefrontal metabolic asymmetries were more frequent in patients with left temporal lobe epilepsy (40.4%) than in those with right temporal lobe epilepsy (13.6%). They have also revealed that frontal lobe cognitive dysfunction, including verbal and performance intelligence measures, correlated with the extent of the hypometabolic regions into the frontal lobes. This suggests that frontal metabolism depicted with [^{18}F]FDG-PET reflects functional deficits in frontal regions and that frontal glucose hypometabolism could be used as a tool to predict frontal dysfunction.

Cerebral plasticity

People with chronic epilepsy are subject to dynamic changes that may lead to functional reorganisation. Cerebral plasticity in epilepsy has been most

extensively evaluated with regard to language function. An interhemispheric shift of language appears to occur leading to right hemisphere language dominance in response to early epileptic lesions in the left (dominant) hemisphere[127, 128]. An intrahemispheric language shift, from primary language areas to adjacent structures, has also been observed[129]. There is a time window, beyond which a transfer of language becomes unlikely[129, 130].

In contrast to language function, plasticity and reorganisation of memory function in epilepsy have been less well investigated. Some evidence suggests that reorganisation of memory function can also occur. Differences in verbal memory deficits after left anterior temporal lobectomy in patients with early and late onset of epilepsy suggest that the patient's age at onset of epilepsy influences cerebral reorganisation of memory functions[100, 101]. Visual memory is often severely impaired in patients with left temporal lobe epilepsy and right hemisphere language dominance whereas verbal memory appears largely preserved[130]. It is understood that right hemispheric substitution or preservation of left hemispheric functions in patients with left hemisphere lesions is mostly achieved at the cost of functions originally lateralised to the right hemisphere[113–115].

Findings from the Wada test support the presence of interhemispheric reorganisation of memory functions after temporal lobe damage[131]. In patients with right temporal lobe epilepsy, memory performance of the left hemisphere was intact independently of the age at which brain damage occurred. In contrast, memory performance of the right hemisphere in patients with left temporal lobe epilepsy was preserved only when brain damage occurred earlier than age 5. This suggests different compensation mechanisms between the left (dominant) and right (non-dominant) hemispheres and the existence of a critical period for interhemispheric reorganisation of memory functions in response to left-sided brain damage.

One fMRI study with encoding tasks for four types of material (patterns, faces, scenes and words) has demonstrated that patients with left temporal lobe epilepsy showed greater verbal encoding activation in the right medial temporal lobe structures, whereas those with right temporal lobe epilepsy showed greater non-verbal encoding activation on the left[132]. This finding also suggests that, in patients with temporal lobe epilepsy, there is reorganisation of memory function to the contralateral medial temporal structures.

Functional reorganisation can also occur in patients who undergo resective surgery. Postsurgical recovery from functional loss can be due to functional takeover by another related system. A substituting system may reside in the ipsilateral hemisphere or in the contralateral homologue of the damaged neural system. Cortical structures including the neocortical lateral temporal structures are phylogenetically newer than medial temporal lobe structures. They provide material-specific functions, which are largely lateralised. In contrast, medial temporal lobe structures are phylogenetically older and provide less material-specific function, which appears to be bilaterally distributed[133]. Therefore, different patterns of functional substitution and compensation may be assumed with regard to functions in archi- and neo-cortical structures after surgery.

One longitudinal [^{18}F]FDG-PET study has shown that glucose metabolism in the ipsilateral lateral temporal lobe was significantly reduced shortly after selective amygdalohippocampectomy, but gradually became normal thereafter[134]. In addition, glucose metabolism in the contralateral medial temporal lobe structures, which was not different from control values preoperatively, was significantly reduced postoperatively and did not recover. Another [^{18}F]FDG-PET study has reported that epilepsy patients with mesial temporal sclerosis showed increased glucose metabolism in the thalamus contralateral to the resection after anterior temporal lobectomy[135]. It is important to learn whether these changes are related to improvement or decline of cognitive functions after surgery.

Thus far, little is known on how removal of medial temporal lobe structures can affect fMRI during memory tasks. There have been few studies with fMRI on memory function considering cerebral plasticity. Identifying the mechanisms of cerebral plasticity may help understand the intersubject variability of cortical representations demonstrated by functional neuroimaging.

CONCLUSION

Despite recent controversies, the Wada test still holds its role as the 'gold standard' in the evaluation of laterality of language and memory for epilepsy surgery. Ideally, the Wada test should be replaced by less invasive, less expensive and less laborious methods that could allow calibration in normal controls. Although recent progress in functional neuroimaging has promised to provide alternative methodologies, this has not yet been achieved. We have reviewed the results from correlative studies between the Wada test and functional neuroimaging modalities ([^{18}F]FDG-PET and fMRI), which indicate that these tests may have potential to support and eventually supersede the Wada test.

Although the laterality of hypometabolism in [^{18}F]FDG-PET is related to memory deficits measured by the Wada test[76–79], the location or spatial

pattern of metabolic changes that can predict impairment of Wada memory performance has not been characterised. If certain cortical regions show a strong correlation between Wada memory scores and [^{18}F]FDG-PET metabolism, presurgical [^{18}F]FDG-PET could play a role in predicting memory laterality during presurgical evaluation.

fMRI has great potential to be a future substitute for the Wada test. Intuitively, predicting the effect of anterior temporal lobectomy on memory processing would best be obtained by using tasks that activate the anterior medial temporal lobe. Event-related fMRI with material-specific multiple tasks appears to be ideal for memory localisation and lateralisation in temporal lobe epilepsy patients. However, the application of findings from fMRI activation is not straightforward, especially in populations with long-lasting intractable epilepsy. Following the development of sensitive activation tasks, verification of the clinical relevance (e.g. relationship to the Wada test, clinical characteristics, pre- and post-surgical neuropsychological measurements and seizure control outcome measurements) is needed before widespread implementation of fMRI for clinical purposes.

We have suggested potential areas for exploring the localisation of memory processing using the Wada test as well as two functional neuroimaging techniques. Since surgery has become more widely available for the treatment of medically intractable epilepsy[18], more patients are expected to undergo presurgical evaluation including those tests. An improved understanding of memory-related brain structures will be of benefit in performing individualised pre- and post-surgical evaluations. This could improve neuropsychological outcome after surgery and guide postoperative neurocognitive rehabilitation as well as presurgical counselling. These studies also have broader implications for neuroscience, in addition to issues involving the management of patients with epilepsy.

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